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Rotavirus vaccine effectiveness stratified by national-level characteristics: an introduction to the 24-country MNSSTER-V Project, 2007–2023

Eleanor Burnett¹, Jazmina Umana², Palwasha Anwari³, Hilda A. Mujuru^{4,5}, Michele J. Groome⁶, Nguyen Van Trang⁷, Volga Iniguez⁸, Stela Gheorghita⁹, Gayane Sahakyan¹⁰, Anvar Nazurdinov¹¹, Fausta Michael¹², Inacio Mandomando¹³, Anne Marie Desormeaux¹⁴, Umid Eraliev¹⁵, Christabel Enweronu-Laryea¹⁶, Cissy Nalunkuma¹⁷, Isidore Bonkoungou¹⁸, Khitam Muhsen¹⁹, Christophe Luhata Lungayo²⁰, Richard Omere²¹, David M Goldfarb²², Annick Lalaina Robinson²³, John McCracken²⁴, Jeannine Uwimana²⁵, Kofi N’Zue²⁶, Gloria Rey-Benito²⁷, Goitom Weldegebriel²⁸, Jason M. Mwenda²⁹, Umesh D. Parashar¹, Jacqueline E. Tate¹ On behalf of the Multi-national subpopulations study to evaluate rotavirus vaccines (MNSSTER-V) project working group

¹Division of Viral Diseases, NCIRD, CDC, Atlanta, GA, USA

²Expanded Program on Immunization, Managua, Nicaragua

³JS Consultancy, Kabul, Afghanistan

⁴Harare Central Hospital, University of Zimbabwe, Harare, Zimbabwe

⁵Department of Paediatrics and Child Health, University of Zimbabwe, Harare, Zimbabwe

⁶Vaccines and Infectious Diseases Analytics Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

⁷National Institute of Hygiene and Epidemiology, Hanoi, Vietnam

⁸Instituto de Biología Molecular y Biotecnología, Universidad Mayor de San Andrés, La Paz, Bolivia

⁹National Center for Public Health, Ministry of Health of the Republic of Moldova, Chisinau, Moldova

¹⁰National Centre of Disease Control and Prevention, Ministry of Health the Republic of Armenia, Yerevan, Armenia

¹¹State Institution “Republican Center of Immunoprophylaxis”, Dushanbe, Tajikistan

Correspondence and reprints: Eleanor Burnett, wwg7@cdc.gov, 1600 Clifton Rd., Atlanta, GA, USA, 30329.

Contributors: JET, UDP, and EB conceived of the project. JMM, GW, GR-B, and DV coordinated the standardized implementation of the WHO protocol across regions. JET and EB lead data acquisition and database management with logistical support from IA. JET and EB developed the analysis plan. EB analyzed the data and lead report writing. EB created the figures with input from AOD. JET and UDP revised early drafts of the manuscript and contributed to data interpretation. All other authors were involved in collecting, managing, assessing quality, analyzing, and/or interpreting the contributing datasets. All authors critically reviewed, edited, and approved the final manuscript for submission.

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- ¹²Ministry of Health, Dar es Salaam, Tanzania
- ¹³Centro de Investigação em Saúde de Manhica (CISM), Maputo, Mozambique
- ¹⁴CDC Country Office, Port-au-Prince, Haiti
- ¹⁵Tashkent Medical Academy, Tashkent, Uzbekistan
- ¹⁶University of Ghana Medical School, Accra, Ghana
- ¹⁷WHO Country Office-Uganda, Kampala, Uganda
- ¹⁸University Joseph KI-ZERBO, Ouagadougou, Burkina Faso
- ¹⁹School of Public Health, Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel
- ²⁰Programme élargi de vaccination, Kinshasa, Democratic Republic of Congo
- ²¹Kenya Medical Research Institute (KEMRI), Centre for Global Health Research (CGHR), Kisumu, Kenya
- ²²University of British Columbia, Vancouver, Canada
- ²³CHU Mère Enfant Tsaralalàna, Antananarivo, Madagascar
- ²⁴Center for Health Studies, Universidad del Valle de Guatemala, Guatemala City, Guatemala
- ²⁵Department of Pathology, Kigali University Teaching Hospital, Kigali, Rwanda,
- ²⁶WHO Country Office- Cote d'Ivoire, Abidjan, Côte d'Ivoire
- ²⁷Pan American Health Organization, Washington DC, USA
- ²⁸WHO/AFRO Inter Country Support Team- East and South, African Region, World Health Organization, Harare, Zimbabwe
- ²⁹Regional Office for Africa (WHO/AFRO), World Health Organization, Brazzaville, Republic of Congo

Abstract

Background: Rotavirus vaccines are moderately protective against illness in high mortality settings compared with low mortality settings. Vaccine effectiveness (VE) evaluations may clarify our understanding of these disparities, but estimates among key subpopulations and against rare outcomes are not available in many analyses due to sample size. We combined 25 datasets from test-negative design case-control evaluations in 24 countries that enrolled children with medically-attended diarrhea, laboratory-confirmed rotavirus stool testing, and documented vaccination status. We calculated rotavirus VE stratified by country-level characteristics.

Methods: Children 3–59 months old with birthdates and surveillance hospital arrival dates were included; other variables were standardized as available. Children were considered vaccinated if they received ≥ 1 dose of rotavirus vaccine >14 days before arrival. We summarized child- and country- level characteristics, including national <5 -year-old child mortality rate (U5M). Following the manufacturer recommended dose schedule, complete- and partial-series adjusted VE were estimated using logistic regression models.

Results: We included 6,626 rotavirus positive children (cases) and 19,459 rotavirus negative children (controls). Adjusted complete series VE was significantly higher among children from countries in the low and medium U5M strata (74% (95%CI: 64–81)) compared to all groups within the high U5M strata (range: 52% (95%CI: 42– 60) to 46% (95%CI: 31–57)). Partial series were lower than complete series estimates.

Conclusions: These findings are consistent with the published literature, though they suggest heterogeneity in vaccine performance within broad child mortality levels. Our findings also highlight the importance of complete-series vaccination.

Summary:

This analysis confirms a significant gradient in rotavirus vaccine performance based on national <5 child mortality rates, where the lowest levels of protection were in the highest mortality settings. We found lower levels of protection with partial series vaccination.

Keywords

Rotavirus; diarrhea; vaccine; immunization; rotavirus vaccine

Introduction

Many oral vaccines, including rotavirus vaccines, provide lower protection from disease to children in low-resource settings than to children in high-resource settings(1). There are four internationally available, World Health Organization (WHO) pre-qualified, live, oral rotavirus vaccines (Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium), Rotasiil (Serum Institute of India Pvt. Ltd., Pune, India), RotaTeq (Merck & Co., West Point, PA, USA), and Rotavac (Bharat Biotech International Ltd., Hyderabad, India)) and 2 nationally licensed live, oral rotavirus vaccines ((Rotavin (PolyVac, Hanoi, Vietnam) and Lanzhou Lamb Rotavirus Vaccine (Lanzhou Institute of Biological Products Co. Ltd., Lanzhou, China))(2). Since their first licensure in 2006 and WHO's expanded implementation recommendation in 2009, rotavirus vaccines have had a tremendous impact on diarrheal disease morbidity and mortality in the >120 countries that have introduced them as part of routine infant vaccination programs(3–7). Randomized controlled clinical trials and post-licensure rotavirus vaccine effectiveness (VE) evaluations have shown a gradient in the level of vaccine-induced protection by national <5-year-old child mortality (U5M) levels, where VE is lower in countries with higher overall U5M and VE is higher in countries with lower overall U5M(8–10). While there are many hypothesized reasons for this disparity including malnutrition, interference from oral polio vaccine, and microbiome differences, data are limited(11). Because diarrhea disease burden is often higher in high child mortality settings than in low mortality settings, even modest protection represents large reductions in illness(12). Despite the success of rotavirus vaccines, rotavirus remains a leading cause of diarrhea hospitalizations among young children globally(13).

Many post-licensure rotavirus VE evaluations have implemented a test-negative case-control design (TND), meaning cases are children who sought healthcare for acute gastroenteritis (AGE) and tested positive for rotavirus and controls are children who sought healthcare

for AGE and tested negative for rotavirus(14). The TND helps ensure cases and controls come from the same source population and have similar healthcare-seeking behaviors and it assumes the controls are representative of the general population. TND evaluations are usually less expensive and simpler to implement than VE evaluations using community or hospital non-diarrhea controls. Rotavirus VE results have been similar when using TND and other control groups in the same settings(15–17). TND has been widely used to evaluate other vaccines, including influenza and COVID-19(14, 18).

To improve vaccine performance and further reduce the burden of hospitalizations and deaths due to rotavirus, there is a need to understand the underlying cause of vaccine performance disparities. We propose calculating VE among various subpopulations and against rare but important outcomes such as death, particularly in countries with high U5M where rotavirus VE is lower. With this information, strategies can be developed to optimize the currently available vaccines and prioritize the design of future rotavirus vaccines. Studies conducted in individual countries typically do not have sufficient sample size to explore VE among small subpopulations and rare outcomes(1, 11). Similarly, literature reviews and meta-analyses are limited by the analyses available(8, 19). The Multi-National Subpopulations Study to Evaluate Rotavirus Vaccines (MNSSTER-V) project aims to address this limitation and estimate VE for these subpopulations and outcomes by pooling child-level data from 25 TND rotavirus VE studies. In this report, we summarize the MNSSTER-V project methods used to combine datasets and present complete and partial series rotavirus VE estimates stratified by country-level characteristics.

Methods

Inclusion criteria

We collaborated with the original data collection and analysis teams from post-licensure rotavirus VE publications of any rotavirus vaccine brand using a TND that recruited children <5 years old with AGE from inpatient wards or emergency departments, using the approach described in a standard protocol from WHO(20). We also contacted teams regarding other unpublished work we were aware of that met the same criteria. In all included datasets, rotavirus disease status was confirmed by enzyme immunoassay (EIA) or immunochromatographic test (ICT) in stool samples (Supplementary table 1) and vaccination status was confirmed by written documentation from the child's home-based vaccination card or clinic register, or by caregiver report if the child had never received any vaccines. The original analysis teams provided final, clean, episode-level analytic datasets. We requested that data on children from 0–59 months be included in the shared dataset, even if the original analysis did not include the full age range; however, this was not available for all datasets. We requested the exclusion of children who were born before rotavirus vaccine introduction, following the original analysis teams' criteria. We requested information regarding the child's demographics, course of illness, symptoms, and socio-economic status, in addition to confirmation of rotavirus testing and vaccination. All children needed dates of birth and arrival to the surveillance hospital, vaccination information, and stool testing results to be included in the combined analytic dataset; all other variables were integrated as they were available.

Because the precise case definitions and documentation of data cleaning varied between the datasets, we applied additional inclusion criteria at the child-level to ensure consistent, standardized inclusion criteria. When data were available, individual children were excluded if diarrhea was ongoing for >7 days before they were admitted to the enrollment hospital (reported or calculated from onset and arrival to the surveillance hospital dates) or if the child experienced <3 episodes of diarrhea in a 24-hour period. If the stool specimens were collected >2 calendar days after arrival, the child was excluded to ensure that rotavirus detected was community-acquired. We also excluded children who had documentation of blood in their stool. While all studies collected written documentation to determine vaccination status, we applied additional standardized criteria to interpret the vaccination data. If the vaccination card or other written documentation showed the date of vaccination >14 days before the date of arrival at the surveillance hospital, the child was considered vaccinated with that dose. This 14-day limit is commonly used to allow time for vaccine-induced immunity to develop. When other concurrently recommended vaccines had dates of administration available, but rotavirus vaccine was not recorded, rotavirus vaccine was considered not to have been given. Finally, children who were reported to never have been vaccinated after birth doses by their caregiver were considered unvaccinated against rotavirus. We excluded children with ambiguous or incomplete written documentation, such as doses marked with check marks instead of dates and children with verbal report of vaccination.

Data management

To generate the final analytic dataset, we standardized variable names and coding. Child's age was calculated from birthdate and surveillance hospital arrival dates. We defined complete and partial vaccination relative to the vaccine brand used by the national immunization program at the time of enrollment. If the country was using a 2-dose rotavirus vaccine (Rotarix or Rotavin), children were completely vaccinated if they had 2 rotavirus vaccine doses meeting our criteria; if they had only 1 dose, they were considered partially vaccinated. If the country was using a 3-dose vaccine (Rotasiil or RotaTeq), children were classified as vaccinated if they had 3 rotavirus doses meeting our criteria; if they had 1 or 2 doses, they were considered partially vaccinated (Supplementary Table 1). Guatemala used Rotarix and RotaTeq during the enrollment period; children enrolled in Guatemala who did not have documentation of which vaccine brand was received or received more than one vaccine brand were included in the analysis of ≥ 1 dose VE analysis and excluded from partial and complete VE analyses.

In addition to variables provided by the original data analysis team, we added several country-level variables for all children. First, countries were categorized by their WHO region (Supplementary Table 1)(21). Secondly, to compare results with recent literature reviews(8, 9), we created child mortality quartiles from the UNICEF 2015 national U5M estimates(22); 2015 was the median year of enrollment for these evaluations. Because there were few countries in our analysis from the "low" or "medium" mortality quartiles (U5M ≤ 16.94 deaths per 1,000 live births), we combined those 2 quartiles into one "low and medium mortality" category (Supplementary Table 2). The remaining countries with U5M >16.94 deaths per 1,000 live births were divided into tertiles. The high U5M tertile included

countries with U5M of 16.95–30.17 deaths per 1,000 live births; the higher U5M tertile included countries with U5M of 30.18–60.47 deaths per 1,000 live births; and the highest U5M tertile included countries with U5M >60.47 deaths per 1,000 live births. Finally, we categorized countries by their 2022 status for funding from Gavi, the Vaccine Alliance (initial self-financing, preparatory transition, accelerated transition, and fully self-financing) (23). Gavi determines the annual level of support available by Gross National Income per capita, with countries in the initial self-financing category receiving the highest level of support and fully self-financing countries receiving no support currently, though the countries in all four groups received support at time of rotavirus vaccine introduction (24). Countries that have never been eligible for Gavi support and Vietnam, which did not receive Gavi support for rotavirus vaccine introduction as part of a demonstration project, were considered a 5th group.

Analysis

We described children 3–59 months old by selected child-level characteristics (calculated age at the arrival to the surveillance hospital, year of enrollment, vaccination status) and country-level variables (WHO region, U5M strata, Gavi status, and vaccine brand used by the national program). Categorical variables are presented as the number of children and percent. Continuous variables are presented as a median and interquartile range (IQR). All variables included in this analysis were available in all contributing datasets.

Our main outcomes were crude and adjusted rotavirus VE and 95% confidence intervals (95% CIs) stratified by country-level variables. VE was calculated as $(1 - \text{odds ratio}) \times 100$. Odds ratios were calculated using unconditional logistic regression. Complete and partial series VE estimates were calculated among children 6–59 months old at the time of hospital arrival. We included children 3–59 months old at the time of hospital arrival to estimate ≥ 1 dose VE. As rotavirus vaccine schedules vary by country (Supplementary Table 1), these age groups allowed children the opportunity to complete the series by 6 months of age or to have received ≥ 1 dose by 3 months of age in all settings as all rotavirus vaccine brands are recommended before these ages and allowed for comparability with other studies. Variables in the adjusted models were selected a priori based on literature reviews and completeness. Adjusted models included the enrollment country, categorized child's age (3–5, 6–11, 12–23, and 24–59 months old), and year of enrollment (2007–2009, 2010–2012, 2013–2015, 2016–2018, 2019–2021, 2022–2023) as confounders. Results from strata that included data from only one country were suppressed. Crude and adjusted VE among children 6–59 months old stratified by country-level categories are presented.

We conducted several sensitivity analyses. First, among datasets where symptom onset date was available, we re-estimated VE where vaccine doses given >14 days before symptom onset were considered valid and compared to VE estimates where doses given >14 days before hospital arrival were counted as valid. As a second sensitivity analysis, we estimated full series VE among children ≥ 8 months old to account for final dose vaccination recommendations at 6 months old in a few countries. Third, for each stratum where one country contributed $\geq 50\%$ of the children, we assigned that country a weight of 0.5 and calculated a weighted adjusted VE for that stratum.

All analyses and data management were performed using SAS v.9.4. Figures were created using the ggplot package(25) in R v4.4.0. This investigation was reviewed by the Centers for Disease Control and Prevention (CDC), deemed not research, and conducted consistent with applicable federal law and CDC policy.

Results

The final analysis included 6,626 children 3–59 months old with AGE who tested positive for rotavirus (cases) and 19,459 children 3–59 months old who tested negative for rotavirus (controls) from 25 datasets collected in 24 countries, 16 of which used Rotarix, 5 used RotaTeq, and 1 each used Rotasiil, Rotavin, and both Rotarix and RotaTeq (Table 1, Supplementary Table 1). The number of children 3–59 months old from each country is visualized in Figure 1. The largest proportion of children were 6–11 months old (n=11,410; 44%), followed by 12–23 months old (n=8,830; 34%). Rotavirus positivity was similar between age groups, ranging from 24% in 3–5 and 6–11 month-old children to 28% in 12–23 and 24–59 month old children. Thirteen countries in the WHO African Region contributed data from 8,562 children; 5 countries in the European Region contributed data from 4,370 children; 4 countries in the Americas Regions contributed data from 7,090 children; and 2 countries from other regions (Eastern Mediterranean and Western Pacific Regions) together contributed data from 6,063 children. Rotavirus positivity ranged from 14% in the European region to 31% in the combined Eastern Mediterranean and Western Pacific regions. Three countries in the combined low and medium U5M quartiles contributed data from 2,818 children. There were 4 countries in the high U5M strata (n=6,955 children), 10 countries in the higher U5M strata (n=9,060 children), and 7 countries in the highest U5M strata (n=7,252 children). Rotavirus positivity increased with U5M strata, from 12% in the low and medium U5M strata to 30% in the highest U5M strata. There were 7 countries contributing data from 6,939 children in Gavi's initial self-financing group; 4 countries contributing data from 4,440 children in the preparatory transition group; 3 countries contributing data from 1,050 children in the accelerated transition group; and 6 countries contributing data from 9,204 children in the fully self-financing group. Among countries whose rotavirus vaccine introduction was supported by Gavi, rotavirus positivity increased from 20% in the currently fully self-financing group to 31% in the initial self-financing group.

Overall, 18,709 children 3–59 months old received a complete rotavirus vaccine series, of which 24% tested positive for rotavirus (Table 1). There were 4,412 children 3–59 months old who received a partial rotavirus vaccine series, of which 25% tested positive for rotavirus, and 2,781 children who did not receive any rotavirus vaccine doses, of which 31% tested positive for rotavirus. Adjusted ≥ 1 rotavirus vaccine dose VE among children 3–59 months old was 50% (95%CI: 45, 55) (Figure 2, Supplementary Table 2). Adjusted complete series VE of any vaccine brand among children 6–59 months old was 53% (95%CI: 48, 58) and partial series VE was 42% (95%CI: 32, 50). For both Rotarix and RotaTeq, complete series VE point estimate was higher than partial series VE (Supplementary Table 2).

The adjusted complete series VE point estimate declined modestly by age group from 56% (95%CI: 48, 62) among children 6–11 months old to 40% (95%CI: 3, 63) among children

24–59 months old (Figure 2, Supplementary Table 2). The low and medium U5M strata had significantly higher adjusted complete series VE (74% (95%CI: 64, 81)) compared to all groups within the high quantiles. Among the high quantile groups, VE point estimates were 50% (95%CI: 38, 60), 52% (95%CI: 42, 60), and 46% (95%CI: 31, 57) in the high, higher, and highest mortality strata, respectively. Partial series VE point estimates were somewhat lower than complete series, decreasing from 66% (95%CI: 38, 81) in the low and medium strata to 37% (95%CI: 13, 55), 37% (95%CI: 20, 51) and 35% (95%CI: 12, 51) in the high, higher, and highest mortality strata, respectively. Complete series rotavirus VE point estimates also declined as the current level of Gavi support increased, from 65% (95%CI: 57, 71) among fully self-financing countries to 44% (95%CI: 29, 56) among initial self-financing countries.

In sensitivity analysis, after excluding 8 datasets that did not include symptom onset date, the adjusted VE was 51% (95%CI: 45, 58) both when doses given >14 days before arrival to the surveillance hospital and when doses given >14 days before symptom onset were considered to be administered. Second, complete series VE among children 8–59 months old was 50% (95%CI: 44, 56) with any vaccine brand, 48% (95%CI: 40, 55) with Rotarix, and 60% (95%CI: 46, 70) with RotaTeq. Finally, 7 strata necessitated a weighted analysis because one country represented 50% of observations (high U5M strata; highest U5M strata; Americas WHO region; initial self-financing, accelerated transition, and fully self-financing Gavi groups; and RotaTeq complete series). The VE point estimate did not change by more than 3 percentage points in any strata when large datasets were down weighted.

Discussion

We found that rotavirus VE was significantly lower in countries with high overall U5M than in countries with low and medium overall U5M. Literature reviews found rotavirus VE to be between 85–95% in low U5M countries, 60–80% in medium U5M countries, and 35–65% in high U5M countries (8, 9). Our results showing 74% VE in low and medium U5M countries and 46–52% VE in the three high U5M strata concur with the published literature, though our analysis was able to estimate VE with more precision. We found VE varied somewhat among the high, higher, and highest U5M strata, suggesting some heterogeneity in vaccine performance within the high mortality groups. Using the Gavi classification of countries, following a different set of criteria based on country income, we found a similar, significant gradient in vaccine performance. The MNSSTER-V dataset's size and the diversity of contributing countries allows for comprehensive consideration of potential drivers of these disparities in rotavirus vaccine performance.

Partial series effectiveness was only 42%, compared to 50% for the complete series. In previous literature reviews and metaanalyses, information about partial dose rotavirus VE was very limited, and, when available, estimates were imprecise(26). Because of the substantial sample size in this dataset, we quantified partial dose series VE with relative precision. Although partial series protection was demonstrated, we found a benefit to complete series vaccination over partial series vaccination with both Rotarix and RotaTeq and at all U5M levels. This information is important for decisionmakers and vaccinators to promote

complete series rotavirus vaccination with any rotavirus vaccine brand to optimize protection and further reduce the burden of rotavirus hospitalizations and deaths.

This pooled dataset of 26,085 children from 25 studies across 24 countries holds promise as the largest global dataset to date to address questions regarding heterogeneity in rotavirus VE estimates in different geographic and socioeconomic settings. Combining multiple datasets allows estimating VE against outcomes and exposures that are not available from individual datasets or meta-analyses. Additionally, this analysis confirms disparities in rotavirus vaccine performance; however, we did not further address the potential causes for differences in VE, such as levels of malnutrition in the population and waning immunity. These reasons require more detailed exploration and analyses than space allows and future analyses of this dataset are planned.

We used logistic regression models for this analysis, rather than fixed or random effects models(27–29). Although there were some differences in quality and cleanliness across the included datasets, the enrollment protocols and designs were essentially identical across studies and any implementation differences were assumed to be comparable to differences between sites in a multi-site evaluation within a single country. The outcome (rotavirus diarrhea) was measured using the same type of test in all but one dataset. For the exposure, we used strict, predefined criteria to interpret and include vaccine card data across sites. Our standardized case definition in this analysis should minimize the impact of enrollment implementation differences between evaluations(20). Sensitivity analyses demonstrated that large datasets did not overwhelmingly influence the VE point estimates or precision.

These findings should be considered alongside a few limitations. First, we assumed all children within a country were vaccinated with the vaccine brand provided through the national immunization program. Although rare, other vaccine brands may have been available on the private market and children who moved between countries may have been vaccinated with another brand. Vaccine brand was not captured during data collection in any country except Guatemala. Similarly, national U5M does not account for in-country heterogeneity and we assumed all children's situations would be reflected in national U5M. Second, only a small number of datasets were available for certain strata and those VE results are not presented. WHO regions in Asia (Eastern Mediterranean, Southeast Asia, and Western Pacific) are notably underrepresented in this analysis, which reflects delayed rotavirus vaccine implementation in many Asian countries. If more datasets become available, particularly from Asian countries or using alternate rotavirus vaccine brands, additional analyses will be informative. Finally, not all variables in the protocol were available from all the datasets, either because the information was not collected or because the original data management team determined the quality was insufficient. For this analysis, we limited variables in the descriptive analysis and in the logistic regression models to those available from all datasets so as not to exclude individual countries. Future analyses using this dataset may choose to maximize the possible confounding variables under consideration in exchange for inclusiveness.

The MNSSTER-V project used a combined dataset to assess rotavirus VE for a range of country-level stratifications. Our findings demonstrated reduced partial series VE compared

to complete series VE and support continued efforts to increase complete series rotavirus vaccine coverage. Finally, these results agree with literature reviews and metaanalyses showing differential rotavirus vaccine performance between high, medium, and low U5M countries. This dataset offers many possibilities to better understand actionable causes of these differences to maximize rotavirus vaccines' impact on diarrhea morbidity and mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The Multi-national subpopulations study to evaluate rotavirus vaccines (MNSSTER-V) project working group:

Yaw Addo, Emmanuel Addo-Yobo, Raymond Adhaku, Iman Ali, Negar Aliabadi, Anyangu Amwayi, Jocelyne Andre-Alboth, Evans Apondi, George E. Armah, Zafarjon Azizov, Julia M. Baker, Neha Balachandran, Joseph Nsiari-muzeyi Biey, Godfrey Bigogo, Ion Birca, Jacques Boncy, Robert F. Breiman, Rachel M. Burke, Jordan Cates, Tyler P. Chavers, Percina Chirinda, Mai Thi Ngoc Chu, Cheryl Cohen, Dani Cohen, Radu Cojocaru, Ingrid Contreras, Margaret M. Cortese, Glavdia Greatchens Delva, Alpha Oumar Diallo, Moshe Ephros, Paul Gastanaduy, Nhamo Archibald Gonah, Svetlana Grigoryan, Nguyen Dang Hien, Gerard Joseph, Jane Juma, Kouadio Sie Kabran, Kathleen Kahn, Ndaye Constant Kapongo, Elias Kassem, Elizabeth Kaudha, Sammy Khagayi, Annet Kisakaye, Renat Latipov, Ly Thi Khanh Le, Eyal Leshem, Benjamin A. Lopman, Shabir A. Madhi, Le Thi Phuong Mai, Filomena Manjate, Loeto Mazhani, Michael Melchior, Margaret Mokomane, Mary C. Moran, Jocelyn Moyes, Manija Mullojonova, Leon Mutesa, Mike J. Mwanga, William M. Mwenge, Esther Nalumasi, Mohammad Zaker Nasery, Kusum Jackson Nathoo, Mwanajuma Ngama, Huong Thuy Nguyen, Marcellin Nimpa, Regina Njeru, John B. Ochieng, Billy Ogwel, Joseph Olore, Clayton Onyango, Grieven P. Otieno, John Samuel Otomba, Betty E. Owor, Nicole A. Page, Gilson Kipese Paluku, Jeff M. Pernica, Thao Thi Phuong Pham, Kimberly D. Pringle, Elisabeth Pukuta, Julia Liliane Raboba, Vonintsoa Lalaina Rahajamanana, Elsa Rakotojoelimaria, Chedelene Riviere, Uri Rubinstein, Babrak Safi, Helah Safi, Najibullah Safi, Sohrab Safi, Akmal Samsor, Shushan Sargsyan, Mapaseka Seheri, Sougue Serge, Andrew P. Steenhoff, Sudoba Suleymonova, Collins Tabu, Ismail Ticklay, Farida Tishkova, Duong Nhu Tran, Dilorom Tursunova, Jennifer R. Verani, Dovile Videbaek, Sibongile Walaza, Catherine Yen, Heather J. Zar

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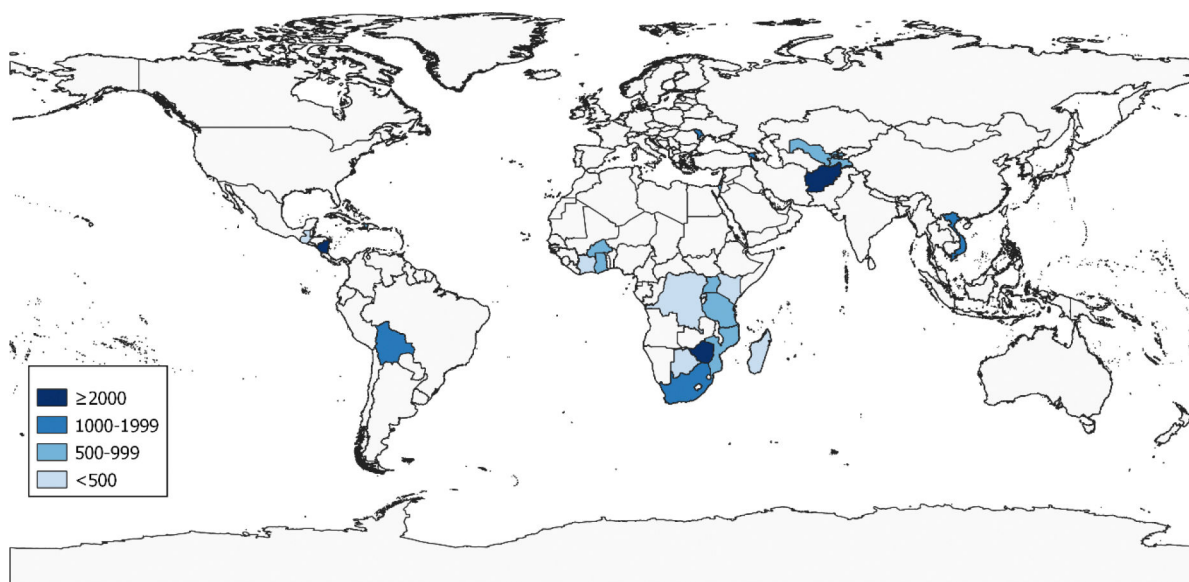


Figure 1.
Number of children 3–59 months old included in the pooled analytic dataset by country,
MNSSTER-V Project.

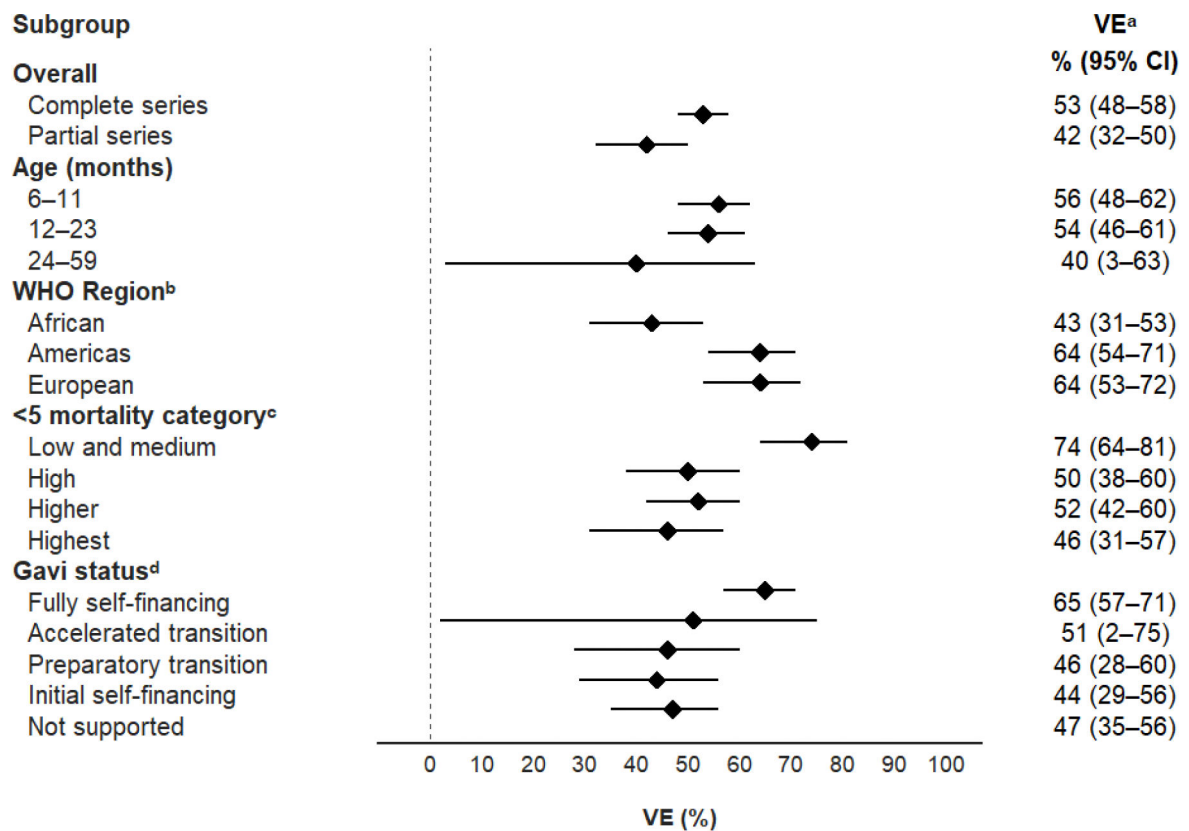


Figure 2.

Adjusted rotavirus vaccine effectiveness against rotavirus diarrhea estimates with 95% confidence intervals (95%CI) for selected subgroups, MNSSTER-V Project.

^a Vaccine effectiveness

^b World Health Organization Region

^c Categorization of 2015 UNICEF overall <5-year-old child mortality estimates

^d 2022 level of Gavi support

Table 1.

Characteristics of children 3–59 months included in the pooled vaccine effectiveness analysis, MNSSTER-V Project.

		Rotavirus positive n=6626		Rotavirus negative n=19459	
		n	%	n	%
Age group	3–5 months	1065	24	3406	76
	6–11 months	2747	24	8663	76
	12–23 months	2435	28	6395	72
	24–59 months	379	28	995	72
Year of arrival to the surveillance hospital	Median, IQR	2015	(2011, 2019)	2015	(2011, 2018)
Country's <5 mortality strata	Highest	2113	30	4842	70
	Higher	2626	29	6434	71
	High	2113	30	4842	70
	Low and medium	329	12	2489	88
World Health Organization region	African	2346	27	6216	73
	Americas	1745	25	5345	75
	European	633	14	3737	86
	Other	1902	31	4161	69
Country's current Gavi status	Initial self-financing	2160	31	4779	69
	Preparatory transition	1094	25	3358	75
	Accelerated transition	273	26	777	74
	Fully self-financing	1884	20	7320	80
	Never eligible or no rotavirus vaccine support	1215	27	3225	73
Rotavirus vaccine brand received	Rotarix	4765	27	13001	73
	RotaTeq	1267	20	4954	80
	Other or unknown	594	28	1504	72
Number of rotavirus doses	≥1 dose	5761	25	17543	75
	Complete series	4573	24	14136	76
	Partial series	1124	25	3288	75
	No doses	865	31	1916	69